Behavioral neurobiology: how larval fish orient towards the light

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DOI: https://doi.org/10.1016/j.cub.2009.12.028

Originally published at:
Mueller, K P; Neuhauss, S C F (2010). Behavioral neurobiology: how larval fish orient towards the light. Current Biology, 20(4):R159-R161.
DOI: https://doi.org/10.1016/j.cub.2009.12.028

Behavioral Neurobiology: How Larval Fish Orient towards the Light

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Current Biology **20**(4): R159-R161

Orientation of animals towards or away from light is a simple behavior commonly found in the animal kingdom. A recent study using zebrafish larvae has revealed the underlying neural logic of this primal choice behavior, by differential use of the retinal ON- and OFF-pathways.

Motile organisms exploring their environment are constantly confronted with a plethora of stimuli that demand the animal to take appropriate decisions. Such navigational decisions are apparent in animals with simple nervous systems and also in neonates, hence at least some decision rules need to be independent of experience and hardwired. For visual animals, the single most important stimulus is a light gradient, which requires the animal to decide whether to veer towards or away from the source of light. This process is called positive or negative phototaxis, depending on its direction. Phototaxis is a widespread phenomenon that is even observed in a rudimental form in prokaryotes. In eukaryotes, phototaxis is thought to have evolved independently at least eight times (Jékely, 2009).

In this issue of *Current Biology*, Burgess et al. (2010) report a study that beautifully dissects the rules leading to the observed behavior of phototaxis in zebrafish larvae. Zebrafish larvae are well suited for such research, as phototactic behavior in this species is expressed early in development, independent of learning and attention, with the added bonus that the zebrafish is a genetically tractable model system with deficient mutant strains available. Zebrafish larvae navigate towards or away from a target light spot using two simple motor patterns — routine turns and slow swims (scoots). During positive phototaxis, larvae first turn towards and thereupon rapidly approach the source of light by an increased frequency of scoot movements compared to baseline activity. In contrast, under negative phototactic conditions, larvae first turn away from the light source and then slowly veer away, but do not exhibit increased scoot rates. The decision to react to a light gradient by positive or negative phototaxis depends on relative target intensity — that is, it depends on both the intensity of the target *and* the pre-adapting light. By dissecting the phototactic response in its constituent parts and revealing the triggering stimuli for each of these, Burgess et al. (2010) found an explanation for this counterintuitive finding.

A promising place to look for a neurobiological basis of phototaxis is the retina. In all vertebrate retinas visual information is channeled into an ON-pathway and an OFF-pathway: the first is activated by an increase of light intensity, while the second is activated by a decrease or dimming of light (Kuffler, 1953; Wu, 1994). In order to test the involvement of these separate retinal pathways, Burgess et al. (2010) made clever use of a mutant line that is selectively disrupted in the ON-pathway. Behavioral analysis of this *no optokinetic response c (nrc)* mutant line (Allwardt et al., 2001; Van Epps et al., 2001) allowed them to separately study the contribution of these two retinal pathways to the phototactic response. In contrast to their wild-type siblings, *nrc* mutants did not show any elevation of scoot movements during positive phototaxis, showing that approaching the target light is mediated by the ON-pathway, and that ‘light ahead’ is the crucial signal to activate the approach mechanism (Figure 1A). This also explains why scoot frequency is not elevated during negative phototaxis, as there is no increase in illumination and therefore no ON-signal is present while the larva swims away from the light source. Pharmacological treatment with either a serotonin reuptake inhibitor or a serotonin receptor antagonist further showed that serotonin signaling is a key part of this neuronal pathway, likely in linking sensory input to motor output.

Showing that the ON pathway mediates approach by triggering increased frequency of scoots immediately raises the question of what role the OFF-pathway may play in phototaxis. Burgess et al. (2010) elegantly showed that the OFF-pathway is responsible for controlling turns. They found that

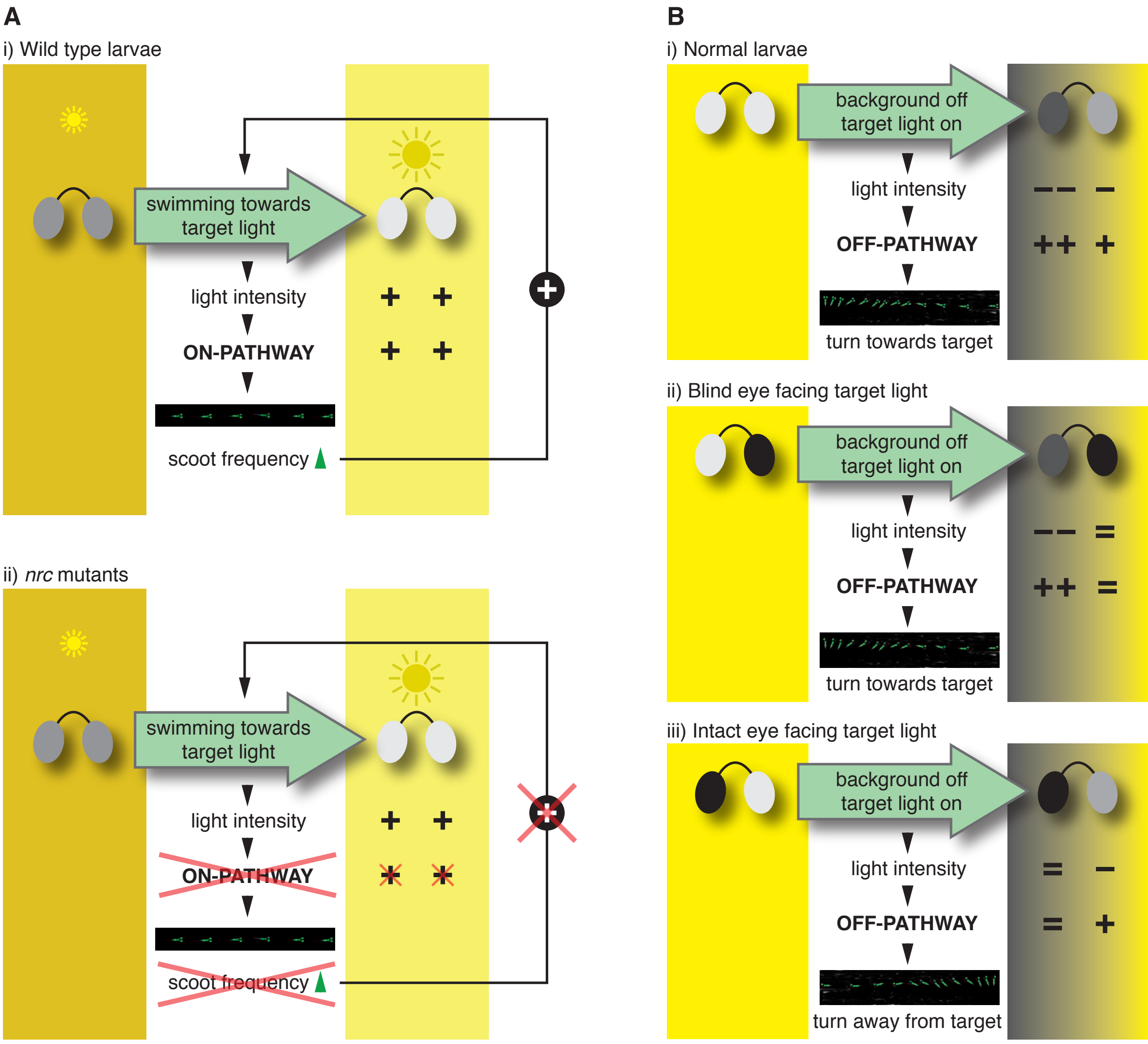

Figure 1: Navigation of zebrafish larvae towards a target light.
(A) Approaching the target light is controlled by the retinal ON-pathway. (i) A simultaneous increase of light intensity in both eyes leads to an increase of scoot frequency in wild-type larvae, forming a positive feedback loop. (ii) Disruption of the ON-pathway in *nrc* mutants prevents increasing scoot frequency, thereby interrupting the feedback loop. *nrc* mutants approach the target light at baseline velocity. (B) Turning towards the target is controlled by the retinal OFF-pathway. (i) Upon switching off bright uniform background illumination, normal larvae orient towards the target light by turning away from the eye experiencing the greater reduction in light intensity. (ii) Unilaterally tectum-ablated larvae facing the target light with their blind eye still turn towards the target light. (iii) In contrast, larvae facing the target light with their intact eye turn away from the target: since the blind eye does not experience a reduc- tion in light intensity, it is the intact eye — although facing the target light — which signals the greater reduction in light intensity.

unilateral optic nerve section or laser ablation of the optic tectum led to normal orientation responses when the target light was in the blind half of the visual field, while reversing the direction of turns when presented in the intact half (Figure 1B). This allowed the authors to draw the following conclusion. When the pre-adapting illumination is switched off, the OFF-pathway triggers turns away from the eye perceiving the stronger reduction in light intensity. As long as the pre-adapting light is brighter than the subsequent target light, this is always the case for the intact eye; therefore, the larva will always turn towards the blind eye.

What happens when the larva is placed between two equally bright target stimuli? The larva now has to choose between two conflicting stimuli. In such a scenario, *Drosophila* would fail to select and approach a single target, but instead would navigate between the two targets (Fraenkel and Gunn, 1961). Not so a zebrafish larva, which navigates towards a single target under such conditions. The authors showed that their OFF-turn/ON-approach algorithm provides a simple mechanism for this behavioral choice. A model based on this algorithm successfully simulated the experimental result.

The activation of turn movements by a decrement in light intensity represents a striking analogy to the situation found in the nematode *Caenorhabditis elegans*. Chalasani et al. (2007) found that withdrawal of an odor stimulus activates interneurons in *C. elegans* which cause an increase of turn movements. Remarkably, the circuit that mediates this behavior in *C. elegans* shares molecular and cellular properties with the vertebrate OFF-pathway, attesting to the ancient evolutionary origin of these behavioral responses.

The new work reported by Burgess et al. (2010) paves the way to unravel the complete neuronal pathway of the phototactic response in zebrafish larvae, including its efferent motor branch. Due to their optical transparency, zebrafish larvae lend themselves to *in vivo* calcium imaging, being able to reveal the activation sequence of neuronal ensembles in a pathway in the behaving larva (Liao and Fetcho, 2008; Orger et al., 2008; Satou et al., 2009). Recent advances in optogenetics, where photoswitchable ion channels and pumps like channelrhodopsin (ChR2) or light-gated glutamate receptors (LiGluR) can be genetically targeted to specific neurons, will allow the dissection of the entire neuronal network mediating this behavior (Arrenberg et al., 2009; Baier and Scott, 2009; Wyart et al., 2009). Neurons suspected to be involved in phototaxis can be activated or inactivated at will to evaluate their contribution to ensuing behavior.

This study (Burgess et al., 2010) beautifully builds on the strength of the zebrafish to understand a simple choice behavior. This is the first step in an exciting journey to understand the whole neural network underlying phototaxis and further studies in this model organism will surely shine light on the mechanism underlying this primal behavior.

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